Title: Digital diary App use for migraine in primary care: prospective cohort study.

Running title: MEDUSA study results

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Ethical standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation (Health Research Authority, UK) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics approval was obtained via Health Research Authority (reference 279980) and Research Ethics Committee (reference 20/YH/0223). Participants consented to participating in the study in line with Declaration of Helsinki on Good Clinical Practice.

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Title: Digital diary App use for migraine in primary care: prospective cohort study.

Abstract

Background

Headache diaries are recommended for migraine management in primary care.

Objective

Determine the acceptability and use of a digital headache diary App for migraine

Methods

Evaluative prospective primary care cohort study in North of England. Part 1 was a postal survey; if responders were interested, in Part 2 participants trialled the digital N1-Headache App headache diary for 90 days, followed by survey feedback on the App's usability.

Results

A total of 637 out of 2189 invited patients (29%) completed the initial survey, and 32% of respondents had previously used a headache diary; 437 out of 637 patients (69%) were interested in using the App. Regression analysis showed that interested patients were those with more severe migraines that limit physical/intellectual activities, and who indicate to not know enough about their migraine. Actual registration numbers and compliance with the App was very modest; 53 out of 173 participants (23%), who ultimately activated their personal N1-Headache

App account, were able to generate a personalised trigger and protector map & report. Furthermore, at the end of the 90 day App trial period there was a non-significant trend towards improvements in participants' health confidence levels.

Conclusion

Migraine patients – particularly those with more severe and frequent migraines - show an interest in using a digital headache diary App, Ultimately, consistent daily use is very modest. The challenge is to improve App usage and compliance rates to allow interpretation of more patients' migraine trigger and/or protector patterns, and wider use amongst patients.

Keywords: migraine, headache diary, health confidence, patient compliance

Title: Digital diary App use for migraine in primary care: prospective cohort study.

Introduction

Headache is one of the most common ailments, with the headache disorder migraine being the fifth leading cause of United Kingdom (UK) years lived with disability [1]. Approximately 10 million people in the UK aged 15 – 69 live with migraine, and 3 million workdays are lost every year in to migraine-related absenteeism alone, at a cost of almost £4.4 billion [2]. The UK annual primary care consultation rate for headache is 4.4 per 100 registered patients, of whom 4% are referred to secondary care for further assessment [3, 4]. UK NICE (National Institute for Health and Care Excellence) Guidance and the National Health Service (NHS) RightCare Headache & Migraine Toolkit recommends the use of headache diaries for the diagnosis and management of migraines [4, 5]. Greater use of headache diaries has also been recommended to help prevent up to 16,500 annual UK emergency hospital admissions for headaches and migraines [4, 6]. However, the following has not been established: although their use is recommended in clinical guidelines, how receptive are patients to using a headache diary if it is offered to them?

This study aimed to determine if a digital headache diary App (Curelator's N1 Headache) is an acceptable tool for patients to monitor migraine in a cohort of primary care patients coded for migraine by their General Practitioner (GP). Patient interest in and use of the App was evaluated, alongside patient perception of App usefulness and trigger and protector identification by its users.

Methods

Study design & patients

This concerns a cohort study (part 1) with an embedded medical device evaluation (part 2), conducted between November 2019 and December 2021. Part 1 involved surveying patients patients aged 16 years or older, who had consulted their GP practice for - and were coded as having - migraine within the last five years. Part 2 involved a subset of part 1 responders (i.e. anyone who was interested) trialling the N1-Headache App for 90 days and then completing a further survey at the end of that period. Patients were recruited from a total of 11 different GP practices in the North of England.

Intervention

Curelator Inc. (Cambridge USA) has developed a proprietary, non-pharmaceutical, digital platform, called N1-Headache; in a series of papers they outlined the methodology behind the identification of potential trigger-attack associations [7, 8, 9]. The App is CE marked as a Class 1 medical device. The N1-Headache App was provided to participants free of charge. Daily data entry (which for each day can be added up to two days later, and is prompted for) is required for 90 days in order to generate sufficient data for profiling of a patient's migraine characteristics. The App does not diagnose headache type, nor recommend medication. A Physician Dashboard web platform, normally used by clinicians, was accessed to determine the number of personalized reports generated.

Outcome measures

The survey contained a checklist for migraine diagnosis tools devised by British Association for the Study of Headache, BASH [10], and International Classification of Headache Disorders, ICHD [11], as well as the patient-reported outcome measure headache impact test (HIT-6, [12]). Furthermore, patients were asked about their health confidence [13] in relation to their migraine, and questions about awareness of migraine diagnosis, previous use of headache diaries, and migraine medication use were included.

For those part 1 responders interested in part 2, written informed consent was obtained before any participant could register and use the N1-Headache App. Participants who signed up for the App were sent three emails during the study (on days 15, 45, and 60) to remind them to continue to use the App. Then, 90 days after signing up for the App, participants were posted another (part 2) survey; this solicited feedback on the App and whether any new triggers were identified, plus it repeated a number of measures from the part 1 survey. The part 2 survey also asked participants about their experience of using the N1-Headache App.

Statistical analyses

For the sample size calculation, a reverse calculation was applied on the basis of survey power. For Part 2 a confidence level of 95% and a confidence interval of 90% was applied, requiring a sample of 96 participants. An anticipated 30% loss to follow-up for part 2 period was taken into account, plus assumption that 33% of Part 1 survey responders were to take part in Part 2. With an initial 20% response rate to the Part 1 survey, 1875 patients would need to be invited. Data was transferred into Excel (Microsoft) and analysed using SPSS (IBM) statistical analysis software. Binary logistic regression analysis and other inferential analyses were applied as indicated in the

Results section (p-value of <0.05 deemed statistically significant). Only completed surveys or surveys with a maximum of one answer missing were included in analyses; for a missing answer the mode (binary data) or median (ordinal data) answer was computed.

Results

An initial 2189 patients were flagged up as having attended a GP consultation concerning migraine in the last 5 years, and being eligible to receive an initial (part 1 of study) postal survey. Of those, 674 patients returned their survey (response rate of 31%; see Figure 1) and of those 637 were sufficiently completed for analysis. Responses to migraine diagnosis questions on self-reported symptoms by the vast majority of patients, 633 out of 637 (99%), matched that of the migraine diagnosis entered by the GP in their medical notes. Only four part 1 participants did not have moderate to severe headaches, with episodes lasting less than 4 hours, and no nausea and/or light or noise sensitivity experienced (see Figure 2); based on patients' own feedback they should therefore not have been invited. Eighty-three percent (n=526 out of 637) of responders were female and 17% (n=111) were male. Age categories were applied and patients from all categories were represented: 83 (13%) responders were aged 16-24 years; 119 (19%) were aged 25-34; 128 (20%) were aged 35-44; 163 (26%) were aged 45-54; 91 (14%) were aged 55-64; 53 (8%) were aged 65 or over. For all 637 responders at baseline, median HIT6 score was 64 (inter-quartile range [IQR] 9) and median HCS was 6 (IQR 4).

At the end of the part1 survey for this study, 437 out of 637 (69%) patients were interested in using the digital N1-Headache headache diary App, see Figure 1. Two hundred and three out of 637 patients (32%) indicated they had previously used a headache diary. Regression analysis

indicates that patients will be particularly interested and in using the N1-Headache App account if: a) their migraines limits physical/intellectual activities, b) they indicate not to know enough about their migraine, and c) their migraines are more severe.

The N1-Headache App's ability to report on potential migraine triggers relies on sustained and daily use of the App by patients for a minimum period of 90 days. Of the 173 patients who activated their personal N1-Headache App account, 53 inputted sufficient data to generate a trigger/protector map. However, we received back a completed part2 day90 survey from 41 of those 53 participants. In the part2 survey, a degree of discrepancy arose where 21 participants claimed (in the survey they completed) to have identified a new trigger as a result of using the N1-Headache App, despite a trigger map & report not being generated due to insufficient daily use. In total, 20 participants who did indeed end up with a trigger summary report reported to have identified one or more *new* triggers for their migraine as a result of using the N1-Headache App. The four most commonly identified triggers were sleep pattern, weather patterns, physical activity, and odours. However, other triggers were also identified such as food types, light and hormonal fluctuations. Figure 3 shows examples of both a trigger and protector map for two different participants.

Migraine-related health confidence score, HCS, was measured both at baseline (part 1 survey) and at the end of the 90-day App use intervention period (part 2/day90 survey). A near statistically significant improvement, assessed with the Wilcoxon test, was achieved for three out of four elements: 'I can look after my migraine health' (p-value 0.11); 'I can get right help for my migraine health' (p-value 0.10); 'I am involved in decisions about my migraine health (p-value 0.16). However, the knowledge element, 'I know enough about my migraine health', showed no

sign of improvement (p-value 0.76) despite it being one of the main reasons for patients showing an interest in trialing the N1-Headache App. The overall total HCS did not change significantly; the median score was 5 (IQR 4) at baseline and a median score of 6 (IQR 5) after 90 days (p-value 0.14, Wilcoxon test). At the end of the 90-day N1-Headache App period, participants were asked for feedback on the application. Table 4 shows that, overall, patients had a positive opinion about (the N1-Headache) digital headache diary App and preferred it over paper diaries even though they did find that it was rather time-consuming to use daily.

Discussion

Recently, the Headache & Migraine Toolkit was introduced by NHS RightCare in the UK [4]. The objective of this toolkit is to enable clinicians to optimise the identification and management of migraine. Headache diaries are seen as a key tool for in understanding the frequency and pattern of attacks, plus the identification of potential triggers and/or protectors of attacks. This present study aimed to determine the interest in and use of a digital headache diary App amongst migraine patients in a primary care setting. Based on the percentage of patients who actually signed up to using the N1-Headache App, 169 out of 2189 invited (7.7%), the interest in the digital diary and its eventual use, 53 out of 2189 invited (2.4%) was very modest. Nonetheless, patients would prefer to use a digital headache diary over a paper version, with the proviso that those who gave feedback on this element was a self-selected cohort of people interested in using the digital headache diary. One objective of the NHS Headache & Migraine Toolkit is to help patients to self-manage their condition after diagnosis. Use of an App may potential enable this and in our study participants' health confidence improved; however, the observed changes were not significant and thus further research would have to explore this theme.

Despite the large sample that was initially screened for and invited to take part in the study, the final part 2 survey sample was small in terms of anticipated survey power; however, the measurement of attrition rates for each step in relation to trialling the N1-Headache App gives real-world outcomes on the feasibility of rolling out a digital headache diary within primary care and NHS. Another limitation of the obtained sample is that it encompasses patients from one region in England with very limited ethnic diversity; on the other hand, both sexes, a wide range of ages and all different deprivation levels are represented. Furthermore, by asking patients about their headache symptoms and profile - using established diagnostic questions from BASH and ICHD [10, 11] – we could confirm that 99% of patients who participated indeed have a migraine disorder. The remaining 1% (four patients) could not be excluded from the part 1 survey since that exact survey was utilised to determine migraine diagnosis based on patient feedback of headache symptoms – none of these four patients ended up using the N1-Headache App.

The N1-Headache App proved useful to monitor true compliance amongst participants. It allowed to detect that some participants reported in the day90 survey that they were sufficiently compliant with daily App use to generate a summary report, yet the true App compliance as monitored via the App's clinician dashboard was much lower. Issues with diary compliance may be an issue for both the paper and digital method [14]. Other researchers have observed compliance (or adherence) to be an issue for digital headache diary Apps. One other study looked at the use of N1-Headache for 90 day – the requisite number of days to enable personal reporting - and found that only half of the 1561 participants made an App entry for 34 or more days [15]. Free-of-charge provision of the App was associated with lower completion rates, which would potentially be a contributing factor for the low completion rates seen in our

present study. Two other studies also reported poor compliance rates in their study cohorts [16, 17]. One challenge will therefore be for App developers to make it 'worthwhile' for patients to complete their daily diary even when they do not have a migraine through e.g. reward systems used in games which have been proven to significantly improve compliance [18].

An in-depth analysis of the per-person number of attacks and detailed overview of the different triggers identified by the N1-Headache App per participant was not an objective of this study, since the App's developer, Curelator, has published extensively about the methodology behind the App and its ability to accurately determine triggers [7, 8, 9]. Patients gave predominantly positive feedback on the usefulness and user-friendliness of the N1-Headache App. Numerous migraine diary Apps have been developed in the last decade, and user-friendliness of some Apps can be an issue, plus sometimes patient and clinical relevance is sub-optimal [19, 20].

Various national healthcare bodies encourage the use of headache diaries to inform patients and clinicians, including general practitioners, about the potential causes of migraine attacks and how to potentially manage or avoid them [4, 5]. Electronic headache diary Apps have more potential than paper diaries to analyse a patient's migraine patterns and feedback from participants in the present study confirms that they former are preferred over the latter [15, 17].

Since many patients – despite high levels of initial interest - either do not sign up to the App, stop using the App, or do not use the App daily, ways need to be found to increase uptake and compliance. Failure to address the App adherence issue may mean too many patients will not experience the potential benefits of a digital headache diary App. To reflect the limited time that clinical staff in primary care have with each patient, in our study no extensive induction took place to help patients familiarise themselves with the N1-Headache App – participants were signposted to utilise the N1-Headche website and in-App instructions. Apart from the

aforementioned ‘in-App’ incentivisation approach [18], directed education of migraine patients concerning digital headache diary App capabilities may further improve take up and compliance. Amongst triptan users, researchers observed that those migraine patients who had previously received education on this family of medications did have better knowledge around their correct use [21]. Finally, in terms of clinicians potentially using digital headache diaries as part of management plans, a more selective approach to which migraine patients are offered an App may be one option. In light of patients with more frequent and severe migraine being more interested in trialling a headache diary App, this could potentially be considered by general practitioners as part of the referral process to a neurologist.

Ethical standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guidelines on human experimentation (Health Research Authority, UK) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics approval was obtained via Health Research Authority (reference 279980) and Research Ethics Committee (reference 20/YH/0223). Participants consented to participating in the study in line with Declaration of Helsinki on Good Clinical Practice.

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Figure Headers:

Figure 1, Flowchart for MEDUSA study

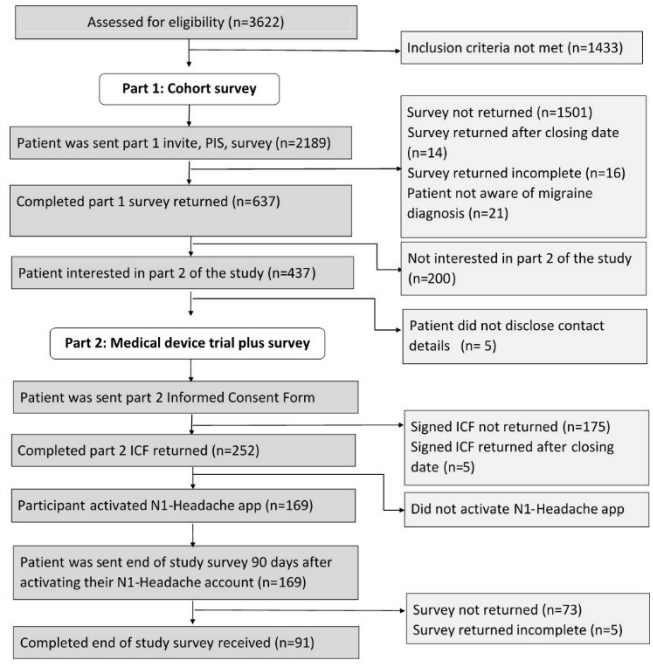


Figure 2, Overview and distribution of migraine symptoms as reported by patients in primary care cohort (total n=637).

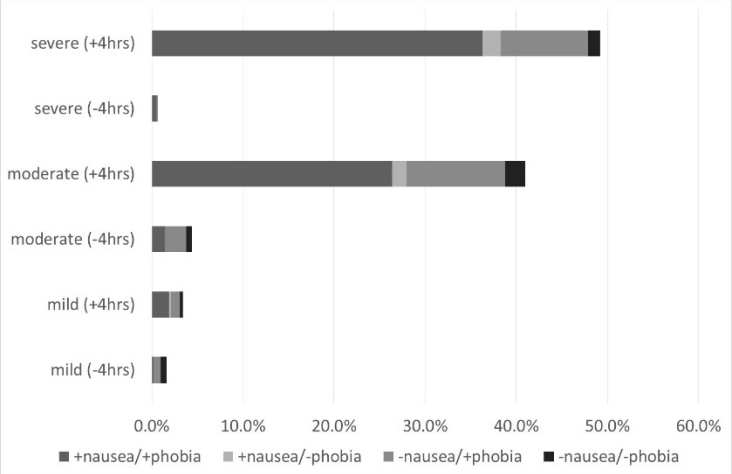
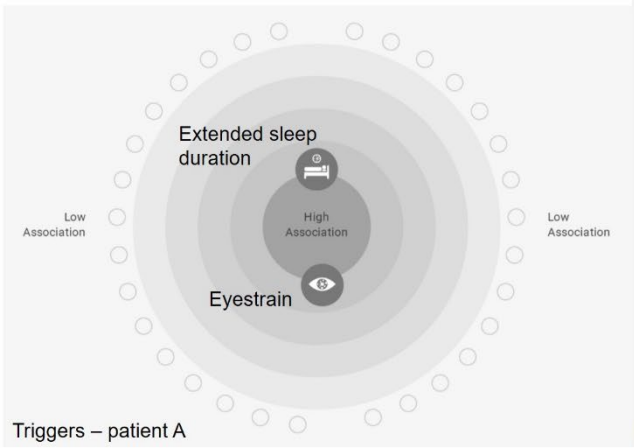
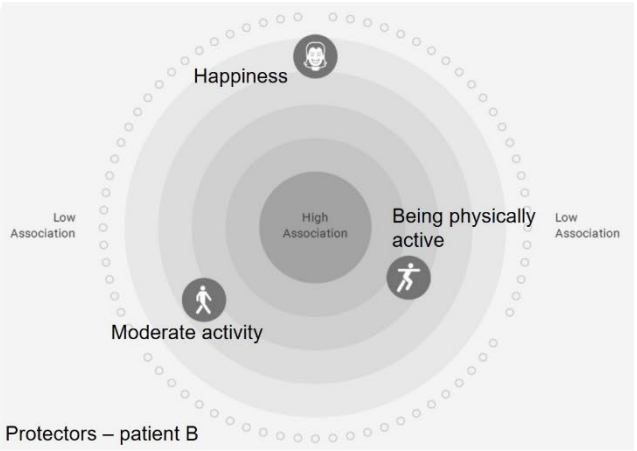


Figure 3, Two examples of N1-Headache App trigger and protector maps generated after 90 days of App use by two respective participants.



Triggers – patient A



Protectors – patient B

Table 1, Variables associated with those migraine patients interested in using N1-Headache headache App, binary logistic regression with backward elimination process.

	Interested in N1-Headache App (no, n = 200; yes, n = 437)		
Variable	**p-value**	**Odds ratio**	**95% CI**
Sex (females)	0.001	0.45	0.29 to 0.73
More than one migraine per month	0.018	1.76	1.10 to 2.81
Migraine limiting daily activities	0.011	2.64	1.25 to 5.58
Migraines are not controlled with medication*	0.033	1.21	1.02 to 1.45
Patient does not know enough about their migraine health	<0.001	0.64	0.51 to 0.79
HIT6 score (increased severity)	0.001	1.05	1.02 to 1.09
Model's final Nagelkerke R2 value	0.23		

95% CI = 95% confidence interval; n.s. = non-significant; *Based on Likert-scale answer to question 'My migraines are well controlled because of the medication(s) that I take'

Table 2, User feedback on N1-Headache diary App

Question	**Distribution of answers (based on n=91 responders)**				
Recommend N1-Headache App	32%; Yes, definitely	41%; Yes, probably	10%; Not sure	13%; No, probably not	4%; No, definitely not
N1-Headache App ease of use	29%; very easy	46%; easy	13%; neither	10%; difficult	2%; very difficult
Patient diary preference	66%; N1-Headache	16%; Other digital App	15%; paper diary	2%; no diary	
How long does it take to use N1-Headache daily	19%; Not long at all	34%; Not really long	41%; Bit too long	7%; Far too long	